REMARKS

Claims 11, 14, 16, 18-24, 26, and 28-42 remain pending in this Application. Claims 11, 16, 18-22, and 36 have been currently amended. Claims 15 and 25 have been canceled without prejudice.

Applicants have amended claims 11 and 36, respectively, to incorporate the limitations of claim 25. In particular, the incorporated limitation is directed to the recombinant N-terminal domain comprising at least 70 amino acids. Applicants have amended claim 16 to remove reference to mutant forms, which include substitutions of free cysteine by other amino acids, and to the alpha domain containing the P3A exon. Applicants have further amended claim 16 to recite that the hydrophobic loops of the subunits corresponding to alpha 128-142 are substituted with the corresponding sequence of the Ach binding protein (AchB). Support for this amendment can be found, for example, on page 8, lines 39 to 43 of the Specification.

"Claims 16, 18-22 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements." The Office Action advises that the claims "only recite 'the alpha, beta, gamma, delta, epsilon subunit comprises amino acids 1-210/1-222/1-224/1-219", which is not clear what specific sequences Applicant intended to use or

refer to." The rejection is hereby traversed and reconsideration is respectfully requested.

Applicants respectfully submit that the claims as previously presented would have been readily understood by one of ordinary skill in the art. For example, a skilled person would readily understand the term "N terminal extracellular domain of the alpha subunit comprises 1-210 amino acids" in claim 18 (previously presented) as meaning that the domain must contain at least all of the first 210 amino acids of the alpha subunit.

Nevertheless, for purposes of expediting prosecution, reference to the domain sequences recited in claims 18 to 22 have been amended to clarify the respective domains as comprising all of the amino acids as recited.

Regarding claim 16, Applicants submit that the rejection no longer applies in view of the amendment to this claim as further discussed below.

Accordingly, Applicants respectfully request that the rejection to claims 16 and 18-22 be withdrawn.

Claims 11, 14-16, 18-26, 36 and 42 stand "rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." The Office Action advises that the "claim(s) contains subject matter which was not described in

the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention application was filed, had possession of the claimed invention." The rejection is hereby traversed and reconsideration is respectfully requested.

Applicants have amended the claims to expedite prosecution. More specifically, the claims as amended refer to amino acid sequences that comprise at least 70 amino acids of the respective alpha, beta, gamma, delta and epsilon domains. As discussed in Applicants' previous response, the sequences of the subdomains of the AChR subunits are extremely well known in the art. A skilled person would have little or no difficulty in identifying sequences that comprises at least 70 amino acids of these subunits.

The present invention relates to the elimination of AChR antibodies due to the combined use of N-terminal domains of the alpha, beta, gamma, delta and epsilon subunits of AChR. A skilled person would readily appreciate that peptides comprising at least 70 amino acids of these domains would be sufficient to provide the utility in the present invention. One skilled in the art could, without undue burden, use a polypeptide comprising at least 70 amino acids of the recombinant N-terminal extracellular domains of alpha, beta, gamma, delta and epsilon subunits to absorb antibodies in the method of the present invention. In this regard, Applicants respectfully point out that the inventive subject matter does not lie in the specific sequence of each domain that is used, but in the fact that domains from all five subunits must be used together.

Applicants further submit that the amendments made to the claims address the objection to mutant forms of AChR subunits. Particularly, reference to the mutant forms which include substitutions of free cysteine by other amino acids and to the alpha domain containing the P3A exon have been removed from claim 16. Regarding the use of FLAG tag mutants and His tags, Applicants respectfully submit that the Examples clearly support use of these constructs. For example, 6His tag mutants are described in Example 1 and FLAG tag mutants are described in Example 2.

Claim 16 has been further amended to recite that the hydrophobic loops of the subunits corresponding to alpha 128-142 are substituted with the corresponding sequence of the Ach binding protein (AchB). This amendment is clearly supported on page 8, lines 39 to 43 of the Specification, which refers to Brejk et al. (Nature, 411, 269-276, 2001). Brejk et al. discloses in detail the structure of AchB and, on page 270, aligns the AchB sequence with pentameric ligand-gated channels, including the alpha domain of AChR. The loops referred to are Cys-Cys loops. The corresponding loop of AchB is the Cys123-Cys136 loop. The Cys-Cys loops are characteristic of all AChR subunits (and AChBP), although the numbering differs somewhat between subunits.

Accordingly, a person of ordinary skill in the art would have no difficulty replacing the hydrophobic loops of the subunits corresponding to alpha 128-142 with the corresponding loop of the AchB domain. In this regard, Applicants respectfully point out that the loops corresponding to alpha 128-142 attach to the membrane part of the

molecule, so they need to be hydrophobic in the intact receptor. In contrast, AChBP is a water-soluble molecule which is homologous to the extracellular part of the AChR. Its corresponding loop is hydrophilic, and thus, when substituted into the AChR domain, results in better expression of the domain. The insertion of the Cys123-136 loop of AchB into the corresponding region of other receptors was previously described in, for example, WO/2001/058951.

Applicants respectfully urge that the aforementioned variants are within the teachings of the present invention, and thus Applicants are entitled to the claim scope which the invention justifies. Accordingly, Applicants respectfully request that this rejection to the claims be withdrawn.

Claims 11, 14-16, 18-26, 36 and 42 stand "rejected under 35 U.S.C. 103(a) as being unpatentable over Psaridi-Linardaki et al. (J.Biol.Chem. 2002. July, 277:26980-26986, cited previously) in view of Barchan et al. (Eur.J.Immunol. 1998. 28:616-624, cited previously), and Besson et al. (Neurology, 1996. 47:1552-1555, cited previously)." The rejection is hereby traversed and reconsideration is respectfully requested.

The present invention addresses the long felt need of providing a safe and effective way of removing antibodies from the serum of Myasthenia Gravis (MG) patients. The method is very effective as it allows the elimination of AChR antibodies due to the combined use of N-terminal domains of the alpha, beta, gamma, delta and epsilon subunits of AChR.

Applicants respectfully submit that Psaridi-Linardaki et al. does not qualify as a prior art reference against the present Application. The present Application is entitled to the benefit of the priority date of April 17, 2002 corresponding to the foreign filing of Greece Patent Application No. 20020100190, which precedes the effective date of the Psaridi-Linardaki reference. Accordingly, Applicants respectfully request that the Psaridi-Linardaki et al. reference be withdrawn from consideration as a prior art reference against the present Application.

Beeson et al. relate generally to the use of a diagnostic assay for identifying MG in patients. Beeson et al. attempted to overcome the problem experienced in 7% of patients of false-negative results in diagnostic assays based on the use of fetal AChR. To overcome this problem, Beeson et al. disclose transfecting TE671 cells with cDNA encoding the human AChR epsilon subunit and generating a stable cell line that expressed an AChR adult subtype suitable for use in diagnostic assays. A diagnostic assay is separate and distinct from immunoadsorption. While the diagnostic assay of Beeson et al. implements the accurate identification of MG sera, the immunoadsorption method of the present invention promotes the purification of the sera from MG antibodies. The applications are not the same. In other words, one skilled in the art would not expect a protein which is effective in a diagnostic context to be also effective in an immunoadsorption context. Beeson et al. does not relate to the purification of serum from an MG patient. The cited reference fails to teach or suggest the use of AChR or its subunits to purify patient serum from MG antibodies or provide further

guidance to one skilled in the art for developing an effective immunoadsorption method to treat MG patients.

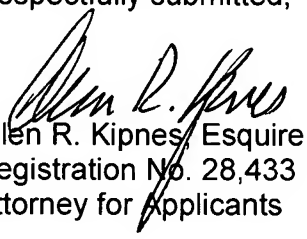
Barchan et al. relate generally to the oral or nasal administration of AChR derived polypeptides for inducing deletion/anergy of antigen-specific T cells. This approach is clearly different from the immunosadsorption method of the present invention. Barchan et al. disclose the use of polypeptides of the extracellular domain of human AChR alpha-unit to modulate the autoimmune response of an individual to the AChR. Barchan et al. fail to teach or suggest the MG antibody binding capacity of the polypeptides or their use for immunoadsorption. Instead, Barchan et al. disclose that the polypeptides bind anti-AChR monoclonal antibodies, and that these polypeptides are capable of protecting mice against experimentally induced MG. The therapeutic approach suggested in Barchan et al. requires in vivo administration and therefore clearly teaches away from the present invention as claimed. Most importantly, Barchan et al. fail to teach or suggest the use of a combination of five AChR subunits.

The cited references, whether taken individually or in combination, fail to teach or suggest to one of ordinary skill in the art the method claimed by Applicants. Accordingly, Applicants' invention as claimed is not anticipated nor made obvious by Beeson et al. in view of Barchan et al. In view of the above remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

Applicants further wish to bring to the Examiner's attention that the U.S. filing date of record the present Application and the spelling of one of the inventors, remain in error. In reference to a submission of June 29, 2005, Applicants have previously requested the issuance of a corrected Filing Receipt to correct the name of one of the inventors from "Loukia Psasridi-Linardaki" to --Loukia Psaridi-Linardaki-- and to the correct the filing date from "May 25, 2005" to --October 18, 2004--. Please note the change in the Filing Date is evidenced by a copy of the date stamped postcard and the Express Mail label receipt enclosed herewith. Applicants have not as of yet received a copy of the corrected Filing Receipt, and respectfully request issuance of the same.

In view of the foregoing, Applicants submit that the present application is in condition for allowance and early passage to issue is therefore deemed proper and is respectfully requested. It is believed that no fees in addition to the fees for the Petition for Extension of Time and the Information Disclosure Statement are due in connection with this matter. However, if any additional fees are due, it should be charged to Deposit Account No. 23-0510.

Respectfully submitted,



Allen R. Kipnes, Esquire
Registration No. 28,433
Attorney for Applicants

Address All Correspondence to:
Allen R. Kipnes, Esquire
WATOV & KIPNES, P.C.
P.O. Box 247
Princeton Junction, NJ 08550
(609)243-0330